C–H Functionalization

One-Pot Synthesis of 2-(Aryl/Alkyl)amino-3-cyanobenzo[b]-thiophenes and Their Hetero-Fused Analogues by Pd-Catalyzed Intramolecular Oxidative C–H Functionalization/Arylthiolation

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Abstract: We have developed a high-yielding synthesis for substituted 2-(aryl/alkyl)amino-3-cyanobenzo[b]thiophenes and their hetero-fused analogues by using a palladium-catalyzed intramolecular oxidative C–H functionalization/arylthiolation reaction of in situ generated N-(alkyl/aryl)thioamides, prepared from readily available (hetero)arylacetonitriles and alkyl/aryl isothiocyanates. This protocol was then extended to the synthesis of amino-substituted benzothieno[2,3-b]quinolines by employing a triflic acid mediated intramolecular cyclocondensation of the prepared 2-arylamino-3-cyanobenzo[b]thiophenes.

Introduction

Substituted benzo[b]thiophenes are a privileged class of heterocycles because of their presence in both synthetic and naturally occurring compounds that have a broad range of biological activity. Selective estrogen receptor modulators (SERMs), acetyl-CoA carboxylase inhibitors, HIV-1 reverse transcriptase inhibitors, antidepressants, and tubulin polymerization inhibitors[1,2] are some examples of the biological properties of compounds that contain the benzo[b]thiophene moiety. These heterocycles also serve as core structures to a host of marketed drugs such as raloxifene, arzoxifene (SERM), and zileuton, a potent and selective inhibitor of 5-lipoxygenase.[1,2] Benzo[b]thiophenes and their condensed analogues are important structural components in the development of optoelectronic materials, including photovoltaics and field-effect transistors.[1,3] Consequently, the synthesis of functionalized benzo[b]thiophenes has been actively pursued in recent years, and many efficient methods have been developed.[1,2,4–6]

Although some 2/3-aminobenzo[b]thiophenes have attracted considerable interest for their biological and physiological effects, these compounds are underdocumented in the literature.[2] 2-Aminobenzo[b]thiophenes are key intermediates in

the synthesis of clinically used drugs such as raloxifene and its analogues,[7] and a few 2-amino-3-substituted benzo[b]thiophenes have been shown to display potent antimitotic and tubulin polymerization inhibitor[8] properties as well as acetyl-CoA carboxylase 1/2 nonselective inhibitor activity.[9] Similarly, a number of 3-[(4-pyridinyl)amino]benzo[b]thiophenes have been found to be selective serotonin reuptake inhibitors, which are useful in the treatment of central nervous system disorders.[10] In view of the biological significance of theses amino-substituted benzo[b]thiophenes, efficient and general methods for the synthesis of these compounds are highly desirable.

Those methods that are reported[11] for the synthesis of 2/3-aminobenzo[b]thiophenes, however, suffer from various drawbacks, such as the need of harsh reaction conditions, including high temperatures, low product yields, unavailable starting materials, the lack of generality of the reaction, and the low substituent diversity. 2-Aminobenzo[b]thiophene has been synthesized in an overall yield of 48 % in five steps from thiosalicylic acid.[11a] Hopkins and Lee-Ruff, on the other hand, reported the synthesis of substituted 2-(dimethylamino)benzo[b]thiophenes in two steps by the treatment of lithium diisopropylamide (LDA) on substituted benzaldehydes and N,N-dimethylthioformamide followed by an acid-mediated intramolecular cyclization of the resulting adduct.[12a] A Lilly research laboratory employed this method for the synthesis of a variety of substituted 2-aminobenzo[b]thiophenes in the development of raloxifene and its analogues.[7a,12b] Substituted 5-nitro-2-alkylaminobenzo[b]thiophenes have been synthesized in low yields (4–47 %) by employing a Willgerodt–Kindler reaction between 2-chloro-5-nitroacetophenone, an alkylamine, and sulfur.[13a] Knochel and co-workers reported two examples of the synthesis of 2-morphilino- and 2-(diphenylamino)benzo[b]thiophenes by using a copper(I)-mediated oxidative cross-coupling reaction of 2-benzothienylzinc reagents with lithium amides of the corresponding amines.[14] Yang and co-workers developed the synthesis of 2-(amino/dimethylamino)benzo-

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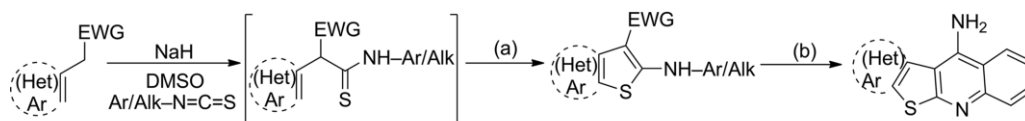http://www.jncasr.ac.in/
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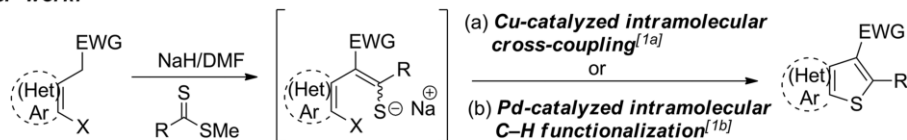
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Scheme 1. Synthesis of substituted benzo[b]thiophenes and thieno-fused heterocycles (EWG = electron-withdrawing group, DMSO = dimethyl sulfoxide, TBAB = tetra-n-butylammonium bromide, DCE = 1,2-dichloroethane).

[b]thiophenes in moderate yields by using the palladium-catalyzed C–S coupling of o-halophenylacetonitriles with $Na_2S_2O_3$ as the sulfur source followed by a one-pot intramolecular thermal cyclization of the resulting 2-mercaptophenylacetonitriles in N,N-dimethylformamide (DMF).[2] 2-(Disubstituted-amino)-3-halobenzo[b]thiophenes have also been obtained by the electrophilic cyclization of o-thioanisole-substituted ynamides with either iodine, N-bromosuccinimide (NBS), or N-chlorosuccinimide (NCS).[15] In a few isolated examples, 2/3-[(alkyl/aryl)-amino]benzo[b]thiophenes have been synthesized in good yields by employing the palladium-catalyzed amination of either (2/3)-halo-[16a,17] or 2-(methylthio)benzo[b]thiophenes.[16b]

During the course of our ongoing studies of synthetic applications for organosulfur intermediates,[18] we recently described the efficient one-pot synthesis of substituted benzo[b]thiophenes and their hetero-fused analogues by involving a sequential base-mediated condensation of substituted 2-bromo(hetero)arylacetonitriles with a range of dithioesters followed by the in situ copper-catalyzed intramolecular C–S arylation of the resulting thioenolate intermediates (Scheme 1).[1a] Subsequently, we reported the one-pot two-step synthesis of highly functionalized benzo[b]thiophenes and their hetero-fused analogues by using a palladium-catalyzed oxidative intramolecular C–H functionalization/C–S bond formation reaction of the in situ generated thioenolates (Scheme 1).[1b] The utility of this method was further demonstrated by the high-yielding synthesis of a raloxifene precursor and tubulin polymerization inhibitor.[1b]

In continuation of these studies, we describe a one-pot approach for the synthesis of substituted 3-cyano-2-(aryl/alkyl)aminobenzo[b]thiophenes and their hetero-fused analogues by using the palladium-catalyzed oxidative intramolecular C–H activation/arylthiolation reaction of N-(alkyl/aryl)thioamides, generated in situ by a base-mediated condensation of (hetero)arylacetonitriles and alkyl/aryl isothiocyanates (Scheme 1). Furthermore, we report the synthesis of amino-substituted benzothieno[2,3-b]quinolines by employing an

acid-mediated intramolecular cyclocondensation of these synthesized 3-cyano-2-(aryl/alkyl)aminobenzo[b]thiophenes.

Results and Discussion

Thioanilide 3a, which was obtained from the reaction of 3-methoxyphenylacetonitrile (1a) and phenyl isothiocyanate (2a) in the presence of sodium hydride in DMSO, was selected as the model substrate in the screening of various catalysts to optimize the reaction conditions to lead to benzo[b]thiophene 4a (Table 1). Thus, thioanilide 3a was subjected to the palladium-catalyzed C–H activation/intramolecular arylthiolation reaction under our previously reported conditions for the synthesis of 2-(hetero)aryl-3-cyanobenzo[b]thiophenes, which involved palladium acetate as the catalyst and cupric acetate or oxygen as the oxidant under various conditions (Table 1).[1b] Benzo[b]thiophene 4a, however, was only obtained in moderate yields under these conditions (Table 1, Entries 1–4). Further screenings of palladium-based catalysts along with various oxidants, solvents, and other changes revealed that the best yields of 4a were obtained in the presence of $PdCl_2$ as the catalyst (20 mol-%), CuI (1.0 equiv.), and Bu_4NBr (2 equiv.) as the additive in DMSO (Table 1, Entry 6). Reducing the catalytic loading to 10 mol-% or the concentration of CuI to 0.5 equiv. did not affect the yield of 4a (Table 1, Entries 7 and 8). However, the yield of 4a decreased considerably by reducing the concentration of Bu_4NBr from 2.0 to 1.0 equiv. (Table 1, Entry 9) and when the reaction was conducted in the presence of oxygen as the oxidant (Table 1, Entry 10).

Having determined the optimal reaction conditions for the conversion of thioanilide 3a into 2-anilino-3-cyanobenzo[b]thiophene (4a; Table 1, Entry 6), we then developed a two-step one-pot reaction protocol by generating thioanilide 3a in situ followed by its direct conversion into benzo[b]thiophene 4a. Thus, when arylacetonitrile 1a and phenyl isothiocyanate 2a were combined in the presence of NaH in DMSO, followed by

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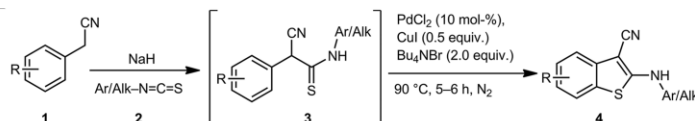Table 1. Optimization studies for the synthesis of benzo[*b*]thiophene **4a** from thioanilide **3a**.[a]
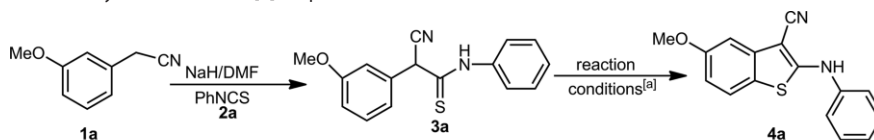
Entry	Catalyst (mol-%)	Oxidant (equiv.)	Additive (equiv.)	Solvent	Yield [%]
1	Pd(OAc)₂ (20)	Cu(OAc)₂ (1.0)	–	DMF[b]	55
2	Pd(OAc)₂ (20)	Cu(OAc)₂ (1.0)	Bu₄NBr (2.0)	DMF	59
3	Pd(OAc)₂ (20)	Cu(OAc)₂ (1.0)	Bu₄NBr (2.0)	DMSO	64
4	PdCl₂ (20)	Cu(OAc)₂ (1.0)	Bu₄NBr (2.0)	DMF	69
5	PdCl₂ (20)	CuI (1.0)	Bu₄NBr (2.0)	DMF	78
6	PdCl₂ (20)	CuI (1.0)	Bu₄NBr (2.0)	DMSO	88
7	PdCl₂ (10)	CuI (1.0)	Bu₄NBr (2.0)	DMSO	86
8	PdCl₂ (10)	CuI (0.5)	Bu₄NBr (2.0)	DMSO	86
9	PdCl₂ (10)	CuI (0.5)	Bu₄NBr (1.0)	DMSO	73
10	PdCl₂ (10)	O₂	Bu₄NBr (2.0)	DMSO	65

[a] Reagents and conditions: the mixture was heated at 90 °C for 5–6 h. [b] The reaction was carried out at 120 °C.

Table 2. One-pot synthesis of 2-(aryl/alkyl)amino-3-cyanobenzo[*b*]thiophenes **4**.[a]

Entry	1	2	4	Yield [%]	Entry	1	2	4	Yield [%]
1	1a	2a	4a	85	7	1e	2a	4g	0
2	1b	2b	4b	82	8	1f	2c	4h	74
3	1c	2a	4c	66	9	1g	2c	4i	88
4	1a	2b	4d	82	10	1g	2b	4j	84
5	1c	2c	4e	68	11	1f	2d	4k	62
6	1d	2a	4f	0	12	1h	2e	4l	82
					13	1g	2f	4m	84
					14	1i	2e	4n, X = H; 4n', X = Br	81; 0

[a] Reagents and conditions: A mixture of **1** (1.0 mmol), **2** (1.0 mmol), and NaH (2.0 mmol) in DMSO (5 mL) was stirred at 0 °C under N₂ for 1 h (progress monitored by TLC analysis) followed by the addition of PdCl₂ (10 mol-%), CuI (0.5 mmol), and Bu₄NBr (2.0 mmol). This mixture was then heated at 90 °C for 5–6 h.
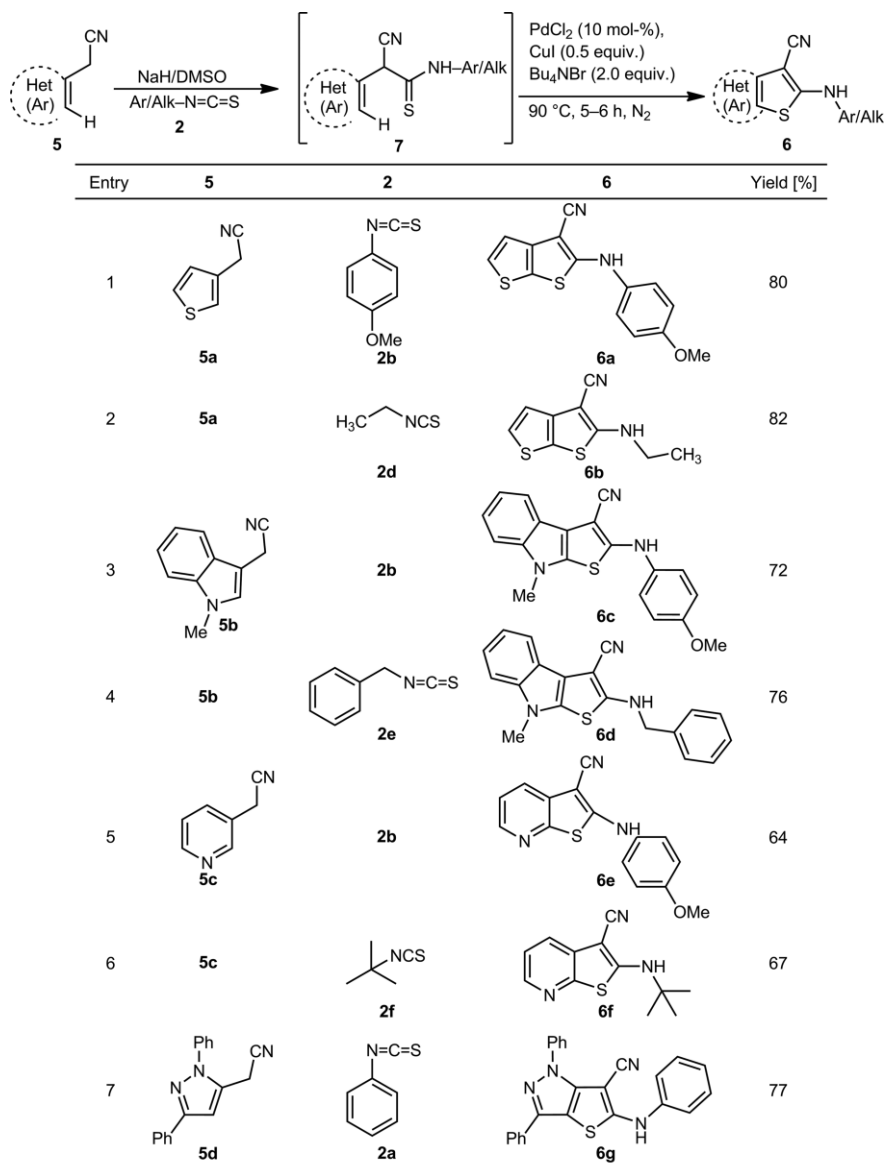
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treatment with PdCl$_2$ (10 mol-%), CuI (0.5 equiv.), and TBAB (2 equiv.) at 90 °C under N$_2$ (progress monitored by TLC), the reaction reached completion within 5 h to furnish benzo[b]thiophene **4a** in a comparable yield of 85 % (Table 2, Entry 1).

With the optimized reaction conditions for the one-pot synthesis of 3-cyano-2-(phenylamino)-5-methoxybenzo[b]thiophene (**4a**) by using the palladium-catalyzed oxidative intramolecular C–H activation/arylthiolation reaction of thioanilide
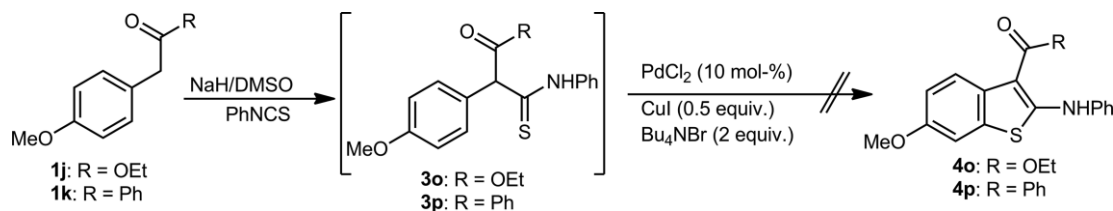
Scheme 2. Attempted synthesis of 2-arylamino-3-(ethoxycarbonyl/benzoyl)benzo[b]thiophene.

Table 3. Synthesis of substituted hetero-fused thiophene **6**.[a]

Entry	5	2	6	Yield [%]
1	5a	2b	6a	80
2	5a	2d	6b	82
3	5b	2b	6c	72
4	5b	2e	6d	76
5	5c	2b	6e	64
6	5c	2f	6f	67
7	5d	2a	6g	77

[a] Reagents and conditions: A mixture of **5** (1.0 mmol), **2** (1.0 mmol), and NaH (2.0 mmol) in DMSO (5 mL) was stirred at 0 °C under N$_2$ for 1 h (progress monitored by TLC analysis) followed by the addition of PdCl$_2$ (10 mol-%), CuI (0.5 mmol), Bu$_4$NBr (2.0 mmol). The mixture was then heated at 90 °C for 5–6 h.

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3a, we then studied the generality and scope of this approach and examined the compatibility of the reaction towards different substituents at various positions on the benzo[*b*]thiophene ring (Table 2). Both electron-donating and electron-withdrawing groups were tolerated on the benzene ring of the various starting arylacetonitriles to yield the corresponding substituted benzo[*b*]thiophenes in good yields (Table 2, Entries 1–5 and 12). However, thioanilides that were derived from arylacetonitriles **1d** and **1e**, which contain electron-withdrawing fluoro or cyano groups that are *para* to the site of cyclization, failed to furnish any of the desired benzo[*b*]thiophenes **4f** and **4g** and yielded only an intractable mixture of products (Table 2, Entries 6 and 7). In contrast, thioanilides that were derived from 3-chloro-acetonitrile (**1f**) easily underwent the palladium-catalyzed intramolecular arylthiolation under similar conditions to furnish the corresponding 5-chloro-substituted benzo[*b*]thiophenes **4h** and **4k** in good yields (Table 2, Entries 8 and 11). These results are in agreement with our earlier observations of palladium-catalyzed oxidative intramolecular arylthiolations of the related dithio-ates.[1b] The corresponding 2-naphthylacetonitrile (**1g**) also underwent the facile one-pot intramolecular C–H activation/aryl-

thiolation reaction in the presence of various isothiocyanates under identical conditions to yield the corresponding 2,3-disub-stituted naphtho[1,2-*b*]thiophenes **4i**, **4j**, and **4m** in high yields (Table 2, Entries 9, 10, and 13). The reaction also proceeded smoothly with various substituted aryl isothiocyanates, such as **2b** and **2c**, as well as alkyl isothiocyanates, such as ethyl, benzyl, and *tert*-butyl isothiocyanates **2d**–**2f**, to form the corresponding 2-alkylaminothiophenes **4k**–**4n** in high yields (Table 2, Entries 11–14). Interestingly, the reaction of 2-bromophenylaceto-nitrile **1i** and benzyl isothiocyanate **2e** under identical conditions, furnished only benzo[*b*]thiophene **4n**, which was formed by intramolecular cross-coupling, and no trace of the corresponding 4-bromobenzothiophene **4n'** was detected in the reaction mixture (Table 2, Entry 14).

An attempted one-pot intramolecular C–H activation/aryl-thiolation reaction of the corresponding thioamides **3o** and **3p**, which were obtained from ethyl 4-methoxyphenylacetate (**1j**) and 2-(4-methoxyphenyl)acetophenone (**1k**), respectively, under identical conditions, did not afford the desired 2-arylamino-3-ethoxycarbonyl- or -3-benzoylthiophenes **4o** and **4p** but yielded only complex mixtures of products (Scheme 2).
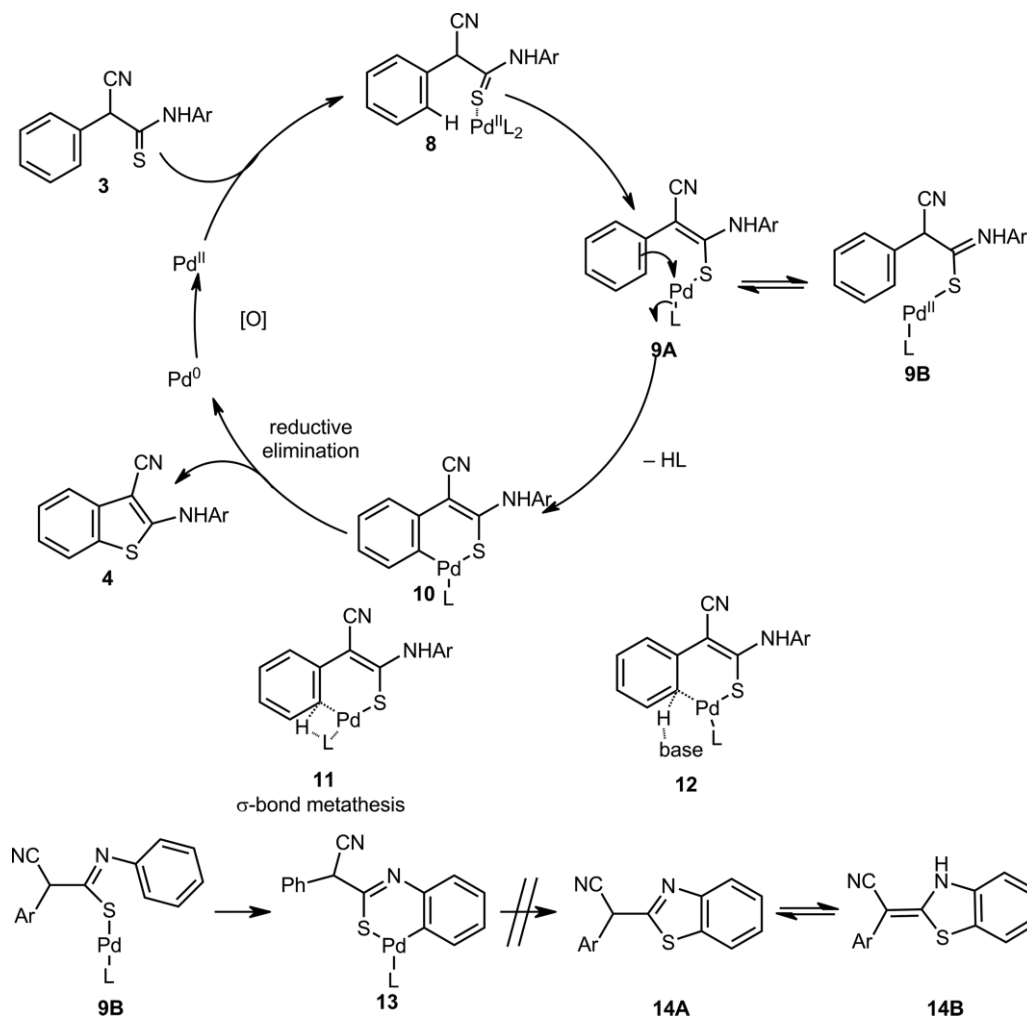
Scheme 3. Plausible mechanism for the formation of 2-aminobenzo[*b*]thiophenes **4** from thioanilides **3**.

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With the successful implementation of the present method towards the synthesis of 2-(aryl/alkyl)amino-3-cyanobenzo[b]thiophenes (Table 2), we next extended this catalytic intramolecular C–H activation/arylthiolation protocol towards the synthesis of the corresponding (aryl/alkyl)amino-substituted hetero-fused thiophenes (Table 3). The intramolecular catalytic C–H activation/(hetero)arylthiolation, amination, and oxygenation of aromatic heterocycles have rarely been investigated.[2] Thus, when thioanilides 7, which were generated in situ from a few selected (hetero)arylacetonitriles such as 3-thienyl-, 3-indolyl-, 3-pyridyl-, and 5-pyrazolylacetonitriles 5a–5d and various isothiocyanates, were subjected to the one-pot palladium-catalyzed intramolecular C–H activation/(hetero)arylthiolation reaction under the optimized conditions (Table 2), the corresponding (aryl/alkyl)amino- and cyano-substituted hetero-fused thiophenes, including thieno[2,3-b]thiophenes 6a and 6b, thieno-[2,3-b]indoles 6c and 6d, thieno[2,3-b]pyridines 6e and 6f, and thieno[3,2-c]pyrazole 6g were obtained in good yields (Table 3, Entries 1–7).

On the basis of these experimental studies, a plausible reaction pathway for the formation of benzo[b]thiophenes 4 from the thioanilides 3 is shown in Scheme 3. The reaction is initiated by the coordination of the sulfur atom to the Pd^{II} atom to lead to the formation of Pd^{II} complexes 8 and 9 followed by an electrophilic palladation to furnish palladacycle 10. The subsequent reductive elimination of 10 leads to the formation of benzo[b]thiophene 4 and a Pd^0 species, which is reoxidized in the presence of copper iodide and Bu$_4$NBr (Scheme 3).[19a] An electrophilic aromatic palladation mechanism is preferred over a σ-bond metathesis or base-assisted deprotonative metalation (to give intermediates 11 and 12, respectively)[19b] because of the electronic effects observed in the reaction. For example, the thioanilides that were derived from arylacetonitriles 1d and 1e, in which there is an electron-withdrawing group (X = F, CN) *para* to the site of the cyclization, failed to furnish benzo[b]thiophenes 4f and 4g, respectively (Table 2, Entries 6 and 7).[1b] Interestingly, the formation of benzothiazoles 14 by an alternative pathway, which proceeds through an intramolecular arylthiolation of Pd complex 9B onto the aromatic ring of the anilide through palladacycle 13, was not observed. We are investigating alternate reaction conditions for the synthesis of 14 from anilides 3 (Scheme 3).

Having accomplished the high-yielding synthesis of various substituted 2-arylamino-3-cyanobenzo[b]thiophenes 4 and their hetero-fused analogues 6, we next considered to utilize benzo[b]thiophenes 4 as precursors in the synthesis of substituted 11-aminobenzothieno[2,3-b]quinolines 15 through an acid-mediated intramolecular cyclocondensation reaction (Table 4). Surprisingly, literature examples for this heterocyclic ring system are rare,[20,21] and the corresponding 11-aminobenzothieno[2,3-b]quinolines are not reported in the literature. These compounds are of pharmaceutical interest as they are thia isosteres of cryptotackiene and ellipticine.[21b] A few of the 11-phenylbenzothieno[2,3-b]quinolines have been synthesized in low yields through a cascade radical reaction of 2-alkynyl-substituted aryl radicals with aryl isothiocyanates and the formation of an α-(arylaminosulfanyl)imidoyl radical as an interme-

diate.[21a] In an isolated example, 7,8,9,10-tetrafluorobenzothieno[2,3-b]quinoline has been synthesized by the acid-catalyzed cyclocondensation of 2-aminobenzo[b]thiophene with pentafluorobenzaldehyde. Unfortunately, its NMR spectra was not recorded because of its insolubility in various solvents.[21b]

Table 4. Synthesis of amino-substituted (benzo/hetero)-fused thieno-[2,3-b]quinolines 15a–15f.[a]

Entry	4 or 6	15	Yield [%]
1	4a	15a	85
2	4c	15b	78
3	4d	15c	80
4	4e	15d	72
5	4j	15e	82
6	6g	15f	70

[a] Reagents and conditions: A mixture of 4 or 6 (1.0 equiv.) and triflic acid (4.0 equiv.) in DCE (5 mL) was heated at 140 °C for 18 h.

We therefore subjected the 2-anilino-3-cyanobenzothiophene 4a to the intramolecular cyclocondensation reaction in the presence of triflic acid at a higher temperature, which afforded the corresponding 2-methoxy-11-aminobenzothieno-[2,3-b]quinoline 15a in 85 % yield (Table 4, Entry 1). Similarly, the corresponding substituted analogues 15b–15d, naphtho-fused 7-amino-9-methoxythieno[2,3-b]quinoline 15e, and 10-amino-1,3-diphenyl-1H-pyrazolo[3′4′:4,5]thieno[2,3-b]quinoline (15f) were also synthesized in high yields from the respective substituted 2-anilino-3-cyanobenzo[b]thiophene 4c–4e, naphtho[1,2-b]thiophene 4j, and 5-anilino-[1H]thieno[3,2-c]-pyrazole 6g (Table 4).[22]

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Conclusions

We have developed an efficient, highly regioselective, one-pot route towards substituted 2-(aryl/alkyl)amino-3-cyanobenzo[*b*]thiophenes and the corresponding hetero-fused analogues by using a palladium-catalyzed oxidative intramolecular C–H functionalization/arylthiolation reaction of the in situ generated *N*-(aryl/alkyl)thioamides from readily accessible precursors. Unlike previous aminobenzothiophene syntheses,[2] this protocol does not require precursors with 2-halo substituents or involve intramolecular cross-coupling reactions. Furthermore, this catalytic intramolecular C–H functionalization/arylthiolation approach can be extended towards the synthesis of (aryl/alkyl)-amino-substituted thieno-fused heterocycles from *N*-substituted thioanilides derived from (hetero)arylacetonitriles. There are notably very few examples in the literature of intramolecular C–H activation/C–heteroatom bond formations to give five- or six-membered heterocycles and lead to fused heterocycles.[1b] In addition, we reported the synthesis of 11-amino-benzothieno[2,3-*b*]quinolines in good yields by using an acid-mediated intramolecular cyclocondensation reaction of the 2-anilino-3-cyanobenzo[*b*]thiophenes **4**. Although there are few reports of their synthesis, these substituted benzothieno[2,3-*b*]quinolines are of pharmaceutical interest. Further work is underway in our laboratory to extend this intramolecular C–H activation/heterocyclization method to other ring systems.

Experimental Section

General Information: All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to standard procedures. The progress of all of the reactions was monitored by thin layer chromatography with standard TLC silica gel plates, and the developed plates were visualized under UV light. Column chromatography was performed on silica gel (100–200 mesh). The NMR spectroscopic data were recorded with a 400 MHz FT-NMR spectrometer, and CDCl$_3$, [D$_6$]DMSO, or CD$_3$OD was used as the solvent. Chemical shifts (δ) are reported in ppm, and the signal of the residual protio solvent was used as the internal standard for ^{1}H NMR (δ = 7.26 ppm for CHCl$_3$, δ = 2.50 ppm for (CD$_2$H)(CD$_3$)SO, and δ = 3.31 ppm for CD$_2$HOD). The deuterated solvent signal was used as the internal standard for ^{13}C NMR (δ = 77.16 ppm for CDCl$_3$, δ = 39.52 ppm for [D$_6$]DMSO, and δ = 49.15 ppm for CD$_3$OD). Coupling constants (*J*) are reported in Hertz. Splitting patterns are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublets), dt (doublet of triplets), td (triplet of doublets), m (multiplet), and br. (broad). Infrared spectra of neat samples were recorded in the ATR (attenuated total reflectance) mode by using an FTIR instrument, and HRMS data were acquired with a Q-TOF spectrometer. Melting points were recorded with an electrothermal capillary melting-point apparatus. All of the required (hetero)arylacetonitriles **1a–1i**[1c] and isothiocyanates **2a–2f**[23] were prepared according to reported procedures.

Procedure for the Synthesis of 2-Cyano-2-(3-methoxyphenyl)-*N*-phenylethanethioamide (3a): To a stirred suspension of NaH (60 % suspension in mineral oil, 80 mg, 2.0 mmol) in DMSO (5 mL) at 0 °C was added a solution of 3-(methoxyphenyl)acetonitrile (**1a**; 147 mg, 1.0 mmol) in dry DMSO (3 mL). After stirring for 10 min, a solution of phenyl isothiocyanate (**2a**; 135 mg, 1.0 mmol) in DMSO (2 mL) was added at 0 °C. The reaction mixture was stirred at room

temperature for 1 h (progress monitored by TLC analysis) and then diluted with a saturated NH$_4$Cl solution (25 mL). The resulting mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with water (3 × 25 mL) and brine (2 × 25 mL) and then dried with Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to give pure **3a** (245 mg, 87 % yield) as a pale yellow semisolid. R_f = 0.3 (EtOAc/hexane, 3:7) ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.77 (br. s, 1 H), 7.55 (d, *J* = 7.6 Hz, 2 H), 7.42–7.36 (m, 3 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.32 (s, 1 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 191.0, 160.8, 138.0, 133.0, 131.1, 129.3, 127.8, 123.7, 121.6, 120.0, 117.1, 115.5, 113.7, 55.6, 55.1 ppm. IR (neat): $\tilde{v}$ = 3324, 1563, 1421, 1103, 748 cm^{-1}. HRMS (ESI): calcd. for C$_{16}$H$_{15}$N$_2$OS [M + H]$^+$ 283.0905; found 283.0885.

Procedure for the Palladium-Catalyzed Intramolecular Oxidative C–H Functionalization/Arylthiolation of Thioanilide 3a. Synthesis of 5-Methoxy-2-(phenylamino)benzo[*b*]thiophene-3-carbonitrile (4a): To a solution of **3a** (282 mg, 1.0 mmol) in dry DMSO (6 mL) were added PdCl$_2$ (18 mg, 0.1 mmol), CuI (95 mg, 0.5 equiv.), and Bu$_4$NBr (644 mg, 2.0 mmol), and the reaction mixture was heated at 90 °C while it was continuously stirred for 5 h (progress monitored by TLC analysis). The reaction mixture was diluted with a saturated NH$_4$Cl solution (25 mL), and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (3 × 25 mL) and brine (2 × 25 mL) and then dried with Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to give the pure benzo[*b*]thiophene (246 mg, 88 % yield) as a pale orange solid; m.p. 181–183 °C. R_f = 0.5 (EtOAc/hexane, 3:7). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.43–7.39 (m, 3 H), 7.35–7.33 (m, 2 H), 7.27 (br. s, 1 H), 7.22–7.18 (m, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 6.84 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.6, 159.1, 140.1, 137.9, 129.9, 125.1, 122.8, 120.9, 120.2, 115.5, 113.1, 103.1, 55.8 ppm. IR (neat): $\tilde{v}$ = 3251, 2198, 1545, 1451, 1293, 758 cm^{-1}. HRMS (ESI): calcd. for C$_{16}$H$_{13}$N$_2$OS [M + H]$^+$ 281.0749; found 281.0745.

General One-Pot Procedure for the Synthesis of Substituted 2-[(Aryl/alkyl)amino]benzo[*b*]thiophenes 4a–4n and Hetero-Fused Thiophenes 6a–6g: To a stirred suspension of NaH (60 % suspension in mineral oil; 40 mg, 2.0 mmol) in DMSO (2 mL) at 0 °C was added dropwise the corresponding (hetero)arylacetonitrile **1a–1i** (1.0 mmol) in DMSO (2 mL). After stirring for 10 min, a solution of the corresponding phenyl isothiocyanate **2a–2f** (135 mg, 1.0 mmol) in DMSO (2 mL) was added to the reaction mixture at 0 °C, and the mixture was stirred at ambient temperature for 1 h. To the reaction mixture were added PdCl$_2$ (18 mg, 0.1 mmol), CuI (95 mg, 0.5 mmol), and Bu$_4$NBr (644 mg, 2.0 mmol), and the reaction mixture was heated at 90 °C and continuously stirred for 5–6 h (progress monitored by TLC analysis). The reaction mixture was diluted with a saturated NH$_4$Cl solution (25 mL), and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (3 × 25 mL) and brine (2 × 25 mL) and then dried with Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (EtOAc/hexane) to give the pure product.

4,7-Dimethoxy-2-[(4-methoxyphenyl)amino]benzo[*b*]thiophene-3-carbonitrile (4b): Brown solid (279 mg, 82 % yield); m.p. 143–145 °C. R_f = 0.62 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28 (d, *J* = 8.0 Hz, 2 H), 6.95 (br. s, 1 H), 6.93 (d, *J* = 8.0 Hz, 2

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H), 6.72 (d, J = 8.0 Hz, 1 H), 6.56 (d, J = 1.2 Hz, 1 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.3, 157.9, 148.3, 147.4, 133.1, 127.6, 124.3, 123.9, 118.1, 116.6, 115.2, 114.6, 107.8, 103.9, 80.7, 56.7, 56.1, 55.7 ppm. IR (neat): $\tilde{v}$ = 3242, 2201, 1548, 1496, 1244, 774 cm^{-1}. HRMS (ESI): calcd. for C$_{18}$H$_{16}$N$_2$O$_3$S [M + H]$^+$ 341.0960; found 341.0955.

6-Fluoro-2-(phenylamino)benzo[*b*]thiophene-3-carbonitrile (4c): White solid (177 mg, 66 % yield); m.p. 174–176 °C. R_f = 0.48 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.2 (s, 1 H), 7.77 (dd, J = 8.0, 4.0 Hz, 1 H), 7.47 (dd, J = 4.0, 4.0 Hz, 2 H), 7.43–7.38 (m, 4 H), 7.27 (dt, J = 12.0, 4.0 Hz, 2 H), 7.18–7.15 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.1, 160.3, 158.7, 140.0, 132.8, 130.1, 130.0, 125.5, 120.9, 120.8, 120.4, 115.1, 114.8, 114.5, 109.0, 108.7, 83.5 ppm. IR (neat): $\tilde{v}$ = 3243, 2208, 1568, 1471, 1252, 750 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_{10}$FN$_2$S [M + H]$^+$ 269.0549; found 269.0550.

2-[4-Methoxyphenyl)amino]-5-methoxybenzo[*b*]thiophene-3-carbonitrile (4d): Yellow solid (254 mg, 82 % yield); m.p. 181–183 °C. R_f = 0.46 (EtOAc/hexane, 2:8). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.01 (br. s, 1 H), 7.59 (d, J = 8.68 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 2.4 Hz, 1 H), 6.81 (dd, J = 8.4, 2.4 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.9, 158.4, 156.9, 138.7, 133.8, 128.2, 123.8, 123.3, 119.7, 115.2, 114.6, 111.5, 102.0, 79.9, 55.3 ppm. IR (neat): $\tilde{v}$ = 3240, 2205, 1598, 1514, 1263, 828 cm^{-1}. HRMS (ESI): calcd. for C$_{17}$H$_{14}$N$_2$O$_2$S [M + H]$^+$ 311.0854; found 311.0843.

2-[4-Chlorophenyl)amino]-6-fluorobenzo[*b*]thiophene-3-carbonitrile (4e): White solid (205 mg, 68 % yield); m.p. 203–205 °C. R_f = 0.49 (EtOAc/hexane, 2:8). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.31 (br. s, 1 H), 7.79 (dd, J = 9.2, 2.4 Hz, 1 H), 7.49 (dd, J = 8.8, 5.2 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 2 H), 7.29 (td, J = 8.4, 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.2, 159.8, 157.8, 139.8, 133.3, 130.0, 129.9, 129.3, 127.9, 121.7, 120.2, 120.1, 114.6, 114.5, 114.2, 109.7, 109.4, 83.0 ppm. IR (neat): $\tilde{v}$ = 3250, 2213, 1567, 1477, 1254, 838 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_8$ClFN$_2$S [M + H]$^+$ 303.0159; found 303.0155.

5-Chloro-2-[(4-chlorophenyl)amino]benzo[*b*]thiophene-3-carbonitrile (4h): Off-white solid (235 mg, 74 % yield); m.p. 207–209 °C. R_f = 0.6 (EtOAc/hexane, 3:7). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.47 (s, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.48–7.46 (m, 2 H), 7.44–7.41 (m, 3 H), 7.30 (dd, J = 9.0 Hz, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.9, 139.5, 138.5, 131.3, 129.4, 128.6, 127.2, 124.4, 123.5, 122.5, 117.9, 114.3, 82.0 ppm. IR (neat): $\tilde{v}$ = 3255, 2209, 1558, 1493, 1293, 758 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_9$N$_2$S [M + H]$^+$ 318.9863; found 318.9860.

2-[4-Chlorophenyl)amino]naphtho[1,2-*b*]thiophene-3-carbonitrile (4i): White solid (294 mg, 88 % yield); m.p. 220–222 °C. R_f = 0.7 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.35 (s, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.54–7.50 (m, 1 H), 7.48–743 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.2, 140.3, 134.7, 130.2, 129.6, 129.3, 127.9, 127.7, 127.4, 125.6, 124.2, 122.6, 121.6, 118.3, 114.8, 86.2 ppm. IR (neat): $\tilde{v}$ = 3249, 2212, 1562, 1494, 1088, 739 cm^{-1}. HRMS (ESI): calcd. for C$_{18}$H$_{17}$N$_2$O$_2$S [M + H]$^+$ 335.0410; found 335.0410.

2-[4-Methoxyphenyl)amino]naphtho[1,2-*b*]thiophene-3-carbonitrile (4j): Off-white solid (277 mg, 84 % yield); m.p. 196–198 °C. R_f = 0.7 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.12 (s, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.55 (d, J = 7.2 Hz, 1 H), 7.49–7.45 (m, 1 H), 7.39 (d, J = 8.8 Hz, 2 H), 7.02 (d, J = 8.8 Hz,

2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.2, 156.9, 135.2, 134.1, 129.7, 129.0, 127.6, 127.5, 127.0, 124.9, 123.6, 122.7, 122.2, 117.9, 114.8, 82.0, 55.3 ppm. IR (neat): $\tilde{v}$ = 3271, 2198, 1557, 1445, 1246, 1035, 798 cm^{-1}. HRMS (ESI): calcd. for C$_{18}$H$_{17}$N$_2$O$_2$S [M + H]$^+$ 331.0905; found 331.0905.

5-Chloro-2-(ethylamino)benzo[*b*]thiophene-3-carbonitrile (4k): Off-white solid (146 mg, 62 % yield); m.p. 210–212 °C. R_f = 0.6 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.46 (d, J = 1.6 Hz, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.09 (dd, J = 8.4, 2.0 Hz, 1 H), 5.49 (s, 1 H), 3.43–3.36 (m, 2 H), 1.38 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.4, 139.3, 132.6, 126.6, 122.9, 122.8, 119.1, 115.5, 42.8, 14.8 ppm. IR (neat): $\tilde{v}$ = 3263, 2196, 1557, 1414, 787 cm^{-1}. HRMS (ESI): calcd. for C$_{11}$H$_{10}$ClN$_2$S [M + H]$^+$ 237.0253; found 237.0240.

2-(Benzylamino)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (4l): Yellow solid (265 mg, 82 % yield); m.p. 152–154 °C. R_f = 0.6 (EtOAc/hexane, 3:7). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.59 (t, J = 8.0 Hz, 1 H), 7.37–7.34 (m, 5 H), 7.29–7.25 (m, 1 H), 6.83 (s, 1 H), 4.49 (d, J = 6.0 Hz, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.3, 148.8, 145.8, 137.8, 130.8, 128.4, 127.3, 119.1, 116.2, 106.2, 101.2, 76.1, 56.0, 55.6, 49.7 ppm. IR (neat): $\tilde{v}$ = 3276, 2193, 1573, 1403, 1253, 771 cm^{-1}. HRMS (ESI): calcd. for C$_{18}$H$_{17}$N$_2$O$_2$S [M + H]$^+$ 325.1011; found 325.1006.

2-(*tert*-Butylamino)naphtho[1,2-*b*]thiophene-3-carbonitrile (4m): Pale yellow solid (235 mg, 84 % yield); m.p. 147–149 °C. R_f = 0.7 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.87 (d, J = 8.0 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H), 7.55–7.51 (m, 1 H), 7.45–7.41 (m, 1 H), 5.24 (s, 1 H), 1.54 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.7, 134.4, 130.2, 129.3, 128.3, 127.2, 127.0, 125.1, 124.8, 122.2, 118.7, 116.0, 83.8, 54.5, 29.3 ppm. IR (neat): $\tilde{v}$ = 3302, 2199, 1539, 1445, 1200, 744 cm^{-1}. HRMS (ESI): calcd. for C$_{17}$H$_{17}$N$_2$S [M + H]$^+$ 281.1112; found 281.1104.

2-(Benzylamino)benzo[*b*]thiophene-3-carbonitrile (4n): Off-white solid (214 mg, 81 % yield); m.p. 165–167 °C. R_f = 0.6 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.88 (t, J = 4.0 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.40–7.34 (m, 4 H), 7.33–7.26 (m, 3 H), 7.12–7.09 (m, 1 H), 4.54 (d, J = 4.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 127.3, 100.0, 98.7, 91.5, 91.2, 90.9, 90.2, 88.6, 85.2, 84.3, 81.9, 78.2, 14.0 ppm. IR (neat): $\tilde{v}$ = 3271, 2195, 1567, 1415, 1350, 745 cm^{-1}. HRMS (ESI): calcd. for C$_{16}$H$_{13}$N$_2$S [M + H]$^+$ 265.0799; found 265.0791.

2-[4-Methoxyphenyl)amino]thieno[2,3-*b*]thiophene-3-carbonitrile (6a): Off-white solid (229 mg, 80 % yield); m.p. 153–155 °C. R_f = 0.7 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.35 (d, J = 5.2 Hz, 1 H), 7.22 (d, J = 8.8 Hz, 2 H), 7.15 (d, J = 5.2 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 6.73 (br. s, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 165.0, 157.6, 141.8, 133.7, 128.2, 123.0, 118.8, 115.5, 115.2, 82.2, 55.7 ppm. IR (neat): $\tilde{v}$ = 3229, 2209, 1549, 1504, 1242, 709 cm^{-1}. HRMS (ESI): calcd. for C$_{14}$H$_{11}$N$_2$OS$_2$ [M + H]$^+$ 287.0313; found 287.0290.

2-(Ethylamino)thieno[2,3-*b*]thiophene-3-carbonitrile (6b): Off-white solid (170 mg, 82 % yield); m.p. 158–160 °C. R_f = 0.72 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.32 (d, J = 8.0 Hz, 1 H), 7.09 (d, J = 5.2 Hz, 1 H), 4.99 (br. s, 1 H), 3.36–3.29 (m, 2 H), 1.36 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.5, 142.5, 127.9, 120.2, 118.7, 116.2, 42.6, 14.8 ppm. IR (neat): $\tilde{v}$ = 3281, 2194, 1557, 1328, 1079, 735 cm^{-1}. HRMS (ESI): calcd. for C$_9$H$_9$N$_2$S$_2$ [M + H]$^+$ 209.0207; found 209.0205.

2-[4-Methoxyphenyl)amino]-8-methyl-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (6c): Off-white solid (240 mg, 72 % yield); m.p. 137–

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139 °C. R_f = 0.6 (EtOAc/hexane, 3:7). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (d, J = 7.6 Hz, 1 H), 7.36–7.29 (m, 2 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.25 (br. s, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 154.9, 154.5, 140.6, 136.8, 132.3, 122.1, 120.0, 119.7, 119.2, 117.4, 115.5, 115.0, 114.8, 110.3, 55.3, 32.1 ppm. IR (neat): ṽ = 3310, 2195, 1506, 1295, 1037, 733 cm^{-1}. HRMS (ESI): calcd. for C$_{19}$H$_{16}$N$_3$OS [M + H]$^+$ 334.1014; found 334.0999.

2-(Benzylamino)-8-methyl-8H-thieno[2,3-b]indole-3-carbonitrile (6d): Pale yellow solid (241 mg, 76 % yield); m.p. 207–209 °C. R_f = 0.6 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.16 (t, J = 6.0 Hz, 1 H), 7.62 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.42 (d, J = 7.2 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 2 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.23–7.19 (m, 1 H), 7.11 (t, J = 7.2 Hz, 1 H), 4.50 (d, J = 6.0 Hz, 2 H), 3.76 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.3, 140.2, 138.2, 128.5, 127.3, 121.4, 119.8, 119.2, 117.1, 116.8, 115.5, 110.2, 73.7, 50.0, 31.9 ppm. IR (neat): ṽ = 3297, 2190, 1557, 1320, 758 cm^{-1}. HRMS (ESI): calcd. for C$_{19}$H$_{16}$N$_3$S [M + H]$^+$ 318.1065; found 318.1058.

2-[(4-Methoxyphenyl)amino]thieno[2,3-b]pyridine-3-carbonitrile (6e): Brown solid (180 mg, 64 % yield); m.p. 187–189 °C. R_f = 0.6 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.31 (dd, J = 4.8, 1.6 Hz, 1 H), 7.76 (dd, J = 8.0, 1.6 Hz, 1 H), 7.31–7.28 (m, 3 H), 7.18 (br. s, 1 H), 6.96 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.0, 158.6, 152.1, 144.9, 132.3, 131.9, 126.3, 124.7, 121.3, 115.3, 114.9, 78.4, 55.7 ppm. IR (neat): ṽ = 3216, 2925, 2206, 1546, 1403, 1248, 790 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_{12}$N$_3$OS [M + H]$^+$ 282.0701; found 282.0699.

2-(tert-Butylamino)thieno[2,3-b]pyridine-3-carbonitrile (6f): Off-white solid (155 mg, 67 % yield); m.p. 113–115 °C. R_f = 0.6 (EtOAc/hexane, 3:7). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (dd, J = 4.8, 1.6 Hz, 1 H), 7.88 (br. s, 1 H), 7.69 (dd, J = 8.0, 1.2 Hz, 1 H), 7.36 (dd, J = 8.0, 4.8 Hz, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.8, 151.6, 143.6, 131.7, 124.9, 121.3, 115.4, 75.4, 54.1, 28.5 ppm. IR (neat): ṽ = 3342, 2922, 2188, 1538, 1407, 787 cm^{-1}. HRMS (ESI): calcd. for C$_{12}$H$_{14}$N$_3$S [M + H]$^+$ 232.0908; found 232.0902.

1,3-Diphenyl-5-(phenylamino)-1H-thieno[3,2-c]pyrazole-6-carbonitrile (6g): White solid (302 mg, 77 % yield); m.p. 241–243 °C. R_f = 0.6 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.33 (s, 1 H), 7.76 (t, J = 7.2 Hz, 4 H), 7.60 (t, J = 8.0 Hz, 2 H), 7.53–7.47 (m, 3 H), 7.45–7.40 (m, 5 H), 7.22–7.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.6, 142.9, 141.6, 140.4, 138.4, 130.9, 129.6, 129.1, 128.6, 128.0, 125.4, 124.7, 123.6, 120.7, 113.5, 105.4, 74.7 ppm. IR (neat): ṽ = 3258, 2209, 1559, 1497, 758 cm^{-1}. HRMS (ESI): calcd. for C$_{24}$H$_{17}$N$_4$S [M + H]$^+$ 393.1174; found 393.1164.

General Procedure for the Synthesis of 11-Aminobenzothieno[2,3-b]quinolines by Acid-Mediated Intramolecular Cyclocondensation. Preparation of 15a–15f: To a solution of benzo[b]thiophenes **4** or **6** (1.0 mmol) in DCE (5 mL), was added triflic acid (0.35 mL, 4.0 mmol) under nitrogen. The reaction mixture was heated at 140 °C for 18 h, then cooled. The excess amount of triflic acid was neutralized by the addition of a saturated solution of NaHCO$_3$. The reaction mixture was diluted with a saturated NH$_4$Cl solution (25 mL), and the resulting mixture was extracted with DCM (3 × 25 mL). The combined organic layers were washed with water (3 × 25 mL) and brine (2 × 25 mL) and then dried with Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to give pure **15a–15f**.

2-Methoxybenzo[4,5]thieno[2,3-b]quinolin-11-amine (15a): Brown solid (238 mg, 85 % yield); m.p. 211–213 °C. R_f = 0.3 (EtOAc/

hexane, 2:3). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.56 (d, J = 8.4 Hz, 1 H), 7.99 (d, J = 2.0 Hz, 1 H), 7.84–7.80 (m, 2 H), 7.70 (t, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.41 (s, 2 H), 7.11 (dd, J = 9.0, 2.0 Hz, 1 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.2, 157.6, 147.9, 147.2, 134.6, 129.7, 127.3, 12.9, 123.1, 122.94, 122.85, 116.0, 112.6, 109.4, 108.6, 55.7 ppm. IR (neat): ṽ = 3493, 3308, 1642, 1574, 1420, 1244, 755 cm^{-1}. HRMS (ESI): calcd. for C$_{16}$H$_{13}$N$_2$OS [M + H]$^+$ 281.0749; found 281.0741.

3-Fluorobenzo[4,5]thieno[2,3-b]quinolin-11-amine (15b): Brown solid (209 mg, 78 % yield); m.p. 224–226 °C. R_f = 0.3 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.58–8.52 (m, 2 H), 7.91 (dd, J = 9.2, 2.4 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 7.72 (t, J = 7.2 Hz, 1 H), 7.49–7.42 (m, 3 H), 7.36 (td, J = 8.8, 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.1, 161.2, 158.8, 147.4, 147.1, 136.6, 136.5, 130.2, 129.7, 127.5, 124.8, 124.7, 123.1, 122.9, 116.1, 112.5, 112.3, 109.9, 109.6, 107.7 ppm. IR (neat): ṽ = 3483, 3318, 1637, 1556, 1271, 745 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_{10}$FN$_2$S [M + H]$^+$ 269.0549; found 269.0543.

2,9-Dimethoxybenzo[4,5]thieno[2,3-b]quinolin-11-amine (15c): Off-white solid (248 mg, 80 % yield); m.p. 231–233 °C. R_f = 0.3 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, CD$_3$OD): δ = 8.23 (d, J = 2.8 Hz, 1 H), 8.19 (d, J = 9.6 Hz, 1 H), 8.14 (m, 1 H), 7.71 (dd, J = 4.0, 2.4 Hz, 1 H), 7.29 (dd, J = 4.0, 2.4 Hz, 1 H), 4.25 (s, 2 H), 4.01 (s, 3 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO): δ = 161.0, 160.4, 159.4, 153.1, 135.2, 135.0, 126.4, 126.4, 125.4, 125.1, 119.8, 118.8, 115.3, 111.0, 110.2, 105.4, 57.1, 56.7 ppm. IR (neat): ṽ = 3571, 3051, 1658, 1563, 1463, 1244, 750 cm^{-1} HRMS (ESI): calcd. for C$_{17}$H$_{15}$N$_2$O$_2$S [M + H]$^+$ 311.0854; found 311.0843.

9-Chloro-3-fluorobenzo[4,5]thieno[2,3-b]quinolin-11-amine (15d): Brown solid (217 mg, 72 % yield); m.p. 227–229 °C. R_f = 0.3 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.71 (s, 1 H), 8.54 (dd, J = 8.8, 5.2 Hz, 1 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.83 (d, J = 8.8 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 7.49 (s, 2 H), 7.38–7.34 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.6, 161.4, 158.9, 146.6, 145.6, 136.8, 136.7, 130.0, 129.81, 129.79, 129.5, 127.7, 125.0, 124.9, 122.0, 116.9, 112.6, 112.4, 109.9, 109.7, 108.2 ppm. IR (neat): ṽ = 3480, 3318, 1596, 1489, 1260, 817 cm^{-1}. HRMS (ESI): calcd. for C$_{15}$H$_9$ClFN$_2$S [M + H]$^+$ 303.0159; found 303.0155.

9-Methoxynaphtho[2′,1′:4,5]thieno[2,3-b]quinolin-7-amine (15e): Off-white solid (270 mg, 82 % yield); m.p. 189–191 °C. R_f = 0.3 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.66 (d, J = 8.4 Hz, 1 H), 8.12–8.05 (m, 3 H), 7.90 (s, 1 H), 7.80 (d, J = 8.8 Hz, 1 H), 7.69–7.61 (m, 2 H), 7.39–7.37 (m, 3 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.3, 155.5, 147.1, 143.0, 131.7, 130.8, 130.76, 129.0, 128.7, 127.7, 127.1, 126.2, 125.3, 124.1, 121.9, 121.8, 116.5, 110.0, 101.7, 55.8 ppm. IR (neat): ṽ = 3480, 3318, 1706, 1507, 1461, 1225, 799 cm^{-1}. HRMS (ESI): calcd. for C$_{20}$H$_{15}$N$_2$OS [M + H]$^+$ 331.0905; found 331.0905.

1,3-Diphenyl-1H-pyrazolo[3′,4′:4,5]thieno[2,3-b]quinolin-10-amine (15f): Yellow solid (274 mg, 70 % yield); m.p. 190–192 °C. R_f = 0.3 (EtOAc/hexane, 2:3). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.23 (d, J = 8.4 Hz, 1 H), 7.89–7.83 (m, 5 H), 7.73–7.72 (m, 4 H), 7.59–7.56 (m, 2 H), 7.47–7.42 (m, 2 H), 6.10 (br. s, 2 H) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO): δ = 167.4, 146.8, 145.6, 142.9, 141.8, 140.3, 131.5, 130.2, 130.1, 129.5, 129.2, 128.4, 127.5, 125.4, 123.5, 122.7, 115.4, 110.9, 101.1 ppm. IR (neat): ṽ = 3463, 3382, 1504, 1455, 1276, 748 cm^{-1}. HRMS (ESI): calcd. for C$_{24}$H$_{17}$N$_4$S [M + H]$^+$ 393.1174; found 393.1164.

Supporting Information (see footnote on the first page of this article): NMR spectra of compounds **4a–4n**, **6a–6g** and **15a–15f**.

[1] a) A. Acharya, S. Vijay Kumar, B. Saraiah, H. Ila, *J. Org. Chem.* **2015**, *80*, 2884, and references cited therein; b) A. Acharya, S. Vijay Kumar, H. Ila, *Chem. Eur. J.* **2015**, *21*, 17116, and references cited therein; c) P. P. Singh, A. K. Yadav, H. Ila, *J. Org. Chem.* **2009**, *74*, 5496, and references cited therein.

[2] C. Hou, Q. He, C. Yang, *Org. Lett.* **2014**, *16*, 5040, and references cited therein.

[3] B. Gabriele, R. Mancuso, E. Lupinacci, L. Veltri, G. Salerno, C. Carfagna, *J. Org. Chem.* **2011**, *76*, 8277, and references cited therein.

[4] For a review, see: B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.* **2011**, *111*, 2937.

[5] a) Z. Wang, W. Geng, H. Wang, S. Zhang, W.-X. Zhang, Z. Xi, *Tetrahedron Lett.* **2011**, *52*, 6997, and references cited therein; b) L. Gao, B. Chang, W. Qiu, L. Wang, X. Fu, R. Yuan, *Adv. Synth. Catal.* **2016**, *358*, 1202.

[6] S. Yugandar, S. Konda, H. Ila, *Org. Lett.* **2017**, *19*, 1512, and references cited therein.

[7] a) T. A. Grese, S. Cho, D. R. Finley, A. G. Godfrey, C. D. C. D. Jones, C. W. Lugar, M. J. Martin, K. Matsumoto, L. D. Pennington, M. Winter, A. M. D. Adrian, H. W. Cole, D. E. Magee, D. L. Phillips, E. R. Rowley, L. L. Short, A. L. Glasebrook, H. U. Bryant, *J. Med. Chem.* **1997**, *40*, 146; b) T. A. Grese, L. D. Pennington, J. P. Sluka, A. M. D. Adrian, H. W. Cole, T. R. Fuson, D. E. Magee, D. L. Phillips, E. R. Rowley, P. K. Shetler, L. L. Short, M. Venugopalan, N. N. Yang, A. L. Glasebrook, H. U. Bryant, *J. Med. Chem.* **1998**, *41*, 1272.

[8] R. Romagnoli, P. G. Baraldi, M. D. Carrion, C. L. Cara, D. Preti, F. Fruttarolo, M. G. Pavani, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. D. Cristina, J. Balzarini, J. A. Hadfield, A. Brancale, E. Hamel, *J. Med. Chem.* **2007**, *50*, 2273.

[9] T. Chonan, D. Wakasugi, D. Yamamoto, M. Yashiro, T. Oi, H. Tanaka, A. Ohoka-Sugita, F. Io, H. Koretsune, A. Hiratate, *Bioorg. Med. Chem.* **2011**, *19*, 1580.

[10] a) R. C. Effland, J. T. Klein, L. L. Martin, G. M. Shutske, K. J. Kapples, J. D. Tomer IV, U.S. Patent 5,328,920, **1994** *Chem. Abstr.* **1995**, *123*, 83210a; b) J. D. Tomer IV, G. M. Shutske, D. Friedrich, *J. Heterocycl. Chem.* **1997**, *34*, 1769.

[11] a) G. W. Stacy, F. W. Villaescusa, T. E. Wollner, *J. Org. Chem.* **1965**, *30*, 4074; b) P. Grandclaudon, A. Lablache-Combier, *J. Org. Chem.* **1978**, *43*, 4379.

[12] a) F. J. Ablenas, B. E. George, M. Maleki, R. Jain, A. C. Hopkinson, E. Lee-Ruff, *Can. J. Chem.* **1987**, *65*, 1800; b) K. Takeuchi, T. J. Kohn, D. J. Sall, M. L. Denny, J. R. McCowan, G. F. Smith, D. S. Gifford-Moore, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 759.

[13] a) A. Y. Solovyev, D. A. Androsov, D. C. Neckers, *J. Org. Chem.* **2007**, *72*, 3122; b) D. A. Androsov, A. Y. Solovyev, M. L. Petrov, R. J. Butcher, J. P. Jasinski, *Tetrahedron* **2010**, *66*, 2474.

[14] a) M. Kienle, A. J. Wagner, C. Dunst, P. Knochel, *Chem. Asian J.* **2011**, *6*, 517; b) C. Dunst, M. Kienle, P. Knochel, *Synthesis* **2010**, 2313.

[15] Y. Kong, L. Yu, L. Fu, J. Cao, G. Lai, Y. Cui, Z. Hu, G. Wang, *Synthesis* **2013**, *45*, 1975.

[16] a) S. Sharif, R. P. Rucker, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, *54*, 9507; *Angew. Chem.* **2015**, *127*, 9643; b) T. Sugahara, K. Murakami, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2014**, *53*, 9329; *Angew. Chem.* **2014**, *126*, 9483.

[17] M.-J. R. P. Queiroz, I. Begouin, I. C. F. R. Ferreira, G. Kirsch, R. C. Calhelha, S. Barbosa, L. M. Estevinho, *Eur. J. Org. Chem.* **2004**, 3679.

[18] For recent papers, see: a) S. Yugandar, S. Konda, H. Ila, *J. Org. Chem.* **2016**, *81*, 2035; b) S. Yugandar, S. Konda, G. Parameshwarappa, H. Ila, *J. Org. Chem.* **2016**, *81*, 5606; c) A. Acharya, S. Vijay Kumar, B. Saraiah, H. Ila, *J. Org. Chem.* **2015**, *80*, 414; d) S. Vijay Kumar, B. Saraiah, H. Ila, *J. Org. Chem.* **2014**, *79*, 7961; e) S. Yugandar, A. Acharya, H. Ila, *J. Org. Chem.* **2013**, *78*, 3948; f) S. Yugandar, N. C. Misra, G. Parameshwarappa, K. Panda, H. Ila, *Org. Lett.* **2013**, *15*, 5250; g) S. Vijay Kumar, G. Parameshwarappa, H. Ila, *J. Org. Chem.* **2013**, *78*, 7362; h) S. Vijay Kumar, S. K. Yadav, B. Raghava, B. Saraiah, H. Ila, *J. Org. Chem.* **2012**, *77*, 10752.

[19] a) K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, *10*, 5147; b) K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya, T. Doi, *Adv. Synth. Catal.* **2010**, *352*, 2643, and references cited therein.

[20] a) L. H. Klemm, R. D. Jacquot, *J. Heterocycl. Chem.* **1975**, *12*, 615; b) C. Camoutsis, P. Catsoulacos, G. Salem, A. Terzis, S. E. Filippakis, *J. Heterocycl. Chem.* **1981**, *18*, 1405.

[21] a) L. Benati, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, G. Zanardi, *J. Org. Chem.* **2000**, *65*, 8669; b) V. O. Iaroshenko, Y. Wang, B. Zhang, D. Volochnyuk, V. Sosnovskikh, *Synthesis* **2009**, 2393.

[22] The attempted acid-mediated intramolecular cyclization of 2-arylamino-thieno[2,3-*b*]thiophene **6a** and the corresponding 2-anilinothieno-[2,3-*b*]indole **6c** did not afford the desired hetero-fused benzothieno-[2,3-*b*]quinolines but yielded complex mixtures of products instead.

[23] J. E. Hodgkins, W. B. Reeves, *J. Org. Chem.* **1964**, *29*, 3098.